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Contribution of spinal cord biopsy to diagnosis of aquaporin-4 antibody positive neuromyelitis optica spectrum disorder

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* *Case contributors to the NEMOS consortium are listed in the Acknowledgments.*

Keywords: Spinal cord tumor, LESCL, spinal biopsy, LETM, neuromyelitis optica, aquaporin-4 antibody

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Abstract

Longitudinally extensive transverse myelitis is characteristic but not pathognomonic for neuromyelitis optica spectrum disorders (NMOSD) and may mimic local tumors. In this retrospective study based on a cohort of 175 NMOSD patients we identified 7 cases who initially presented with a longitudinally extensive spinal cord lesion and underwent spinal cord biopsy due to MRI-suspected malignancies. Remarkably, routine neuropathology was inconclusive and did not guide the diagnostic process to anti-aquaporin-4 (AQP4)-seropositive NMOSD. Serious postoperative complications occurred in 5/7 patients and persisted during follow-up in 2/7 patients (29%). Considering these sequelae, AQP4-antibody testing should be mandatory in patients with inconclusive longitudinally extensive spinal cord lesions prior to biopsy.

Introduction

Neuromyelitis optica (NMO) is an inflammatory demyelinating autoimmune disease with the key features optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM), characterized by a spinal cord MRI lesion ≥ 3 vertebral segments.[1,2] However, LETM is not pathognomonic for NMO spectrum disorders (NMOSD),[1] as longitudinally extensive spinal cord lesions (LESCL) can be observed with coexisting systemic autoimmune diseases, infections, vascular and metabolic disorders, and following irradiation.[3-5] Moreover, intramedullary tumors or paraneoplastic myelopathies may present as LESCL and thus mimic NMO-associated LETM.[3,4] Usually, clinical history and presentation, neuroimaging findings as well as cerebrospinal fluid (CSF) and serological tests guide the diagnostic work-up of NMOSD,[6,7] particularly after the recent discovery of highly specific anti-aquaporin4-antibodies (AQP4-Ab).[8] However, in rare cases the identification of the underlying pathology is difficult, rendering spinal cord biopsy with potentially serious sequelae an ultimate means to rule out malignancies. Here, we retrospectively investigated the incidence and diagnostic value of spinal cord biopsy as well as the subsequent clinical outcome within a recently reported cohort of NMOSD patients.[7]

Methods

To identify NMOSD patients who underwent spinal cord biopsy we used the German Neuromyelitis Optica Study Group as previously described (www.nemos-net.de).[9] At the time of analysis, 175 NMOSD cases as defined by Wingerchuk and colleagues (2007)[1] had been captured.[7] Patients who underwent biopsy had been transferred for follow-up from neurosurgical and neurological hospitals to the Departments of Neurology in Düsseldorf or Berlin, Germany, and Hochegg, Austria, respectively. We were able to perform a neuropathological reevaluation in 4/7 cases, using the original biopsy specimen. The study was approved by the local ethics committees, and all patients gave written informed consent.

Results

We identified seven female NMOSD patients with a prior history of diagnostic spinal biopsy, 6 of Caucasian, 1 of Afro-American origin, while the other patients of our cohort did not undergo spinal biopsy. None of the patients had a prior brain biopsy. The median age was 40 years (range 24-52) at first clinical presentation and 43 years (range 29-57) at LETM/biopsy. LETM was the initial manifestation in 4 patients, 3 patients had experienced an inflammatory episode suggestive of NMOSD prior to biopsy (optic neuritis or rhombencephalitis; Table). Suspected diagnoses leading to biopsy 84 days after clinical onset (mean; range 8 days-10 months) included “astrocytoma”, “atypical pen-like glioma”, “tumor of unknown etiology”, “spinal tumor” and “intramedullary tumor”. Spinal MRI showed non-homogeneous gadolinium enhancement (in 6/7 patients) with pronounced myelon swelling between the medulla oblongata and Th9 (range), extending >6 segments (mean, range 4-15; Figure). Brain MRI prior to biopsy was normal in 4/7 patients or revealed unspecific white matter lesions in 3/7 cases. CSF analysis showed mild (5/7 patients) or moderate pleocytosis (2/7 patients) and isolated oligoclonal bands in one patient (Table).

Remarkably, initial histopathological diagnoses did not suggest an NMO-related process but were reported as 1) “inflammatory destructive lesion”, 2) “glial tumor with desmoplastic and angiogenic compound of low malignancy”, 3) “angiodysgenetic necrotizing myelopathy Foix-Alajouanine”, 4) “subacute necrosis, no tumor”, 5) “tumor-free spinal cord”, 6) “CNS tissue with severe reactive and resorptive changes, no neoplasia” and 7) “reactive CNS tissue with inflammation and resorptive changes” (Table).

Reevaluation of four available biopsies was limited by the small sample size and numbers of sections. Demyelination was evident in all cases. Inflammation (CD3), extensive axonal damage (Bielschowsky silver impregnation) and hyalinized vessels were evident in 3/3 biopsies. Perivascular complement depositions were not found (0/3; C9neo) and complement

within macrophages was evident in one case (1/3; C9neo). Only in one biopsy were eosinophilic granulocytes present. Both of the 2 cases in which GFAP and AQP4 could be stained showed astrocytic dystrophy and loss as well as loss of AQP4. Oligodendrocytes (NOGO-A or CNPase staining) were depleted in 2/2 biopsies (see supplemental Figure).

All patients were AQP4-seropositive when tested after biopsy using cell-based assays. The final diagnoses were NMO (4/7) and NMO-related LETM (3/7) at an average of 68.4 months (range 0.5-160) after initial symptoms and 30.3 months (range 0.25-103.5) after biopsy (Table). Notably, 3 patients were biopsied before AQP4-Ab testing was routinely available (one in 1995, two in 2002).[8] Testing was available but not performed before surgery in all other cases. Median EDSS prior to biopsy was 4.0 (range 2.5-8.0) and 8.0 (range 3.0-8.5) in the first few days thereafter, due to severe complications like CSF leakage, epidural hematoma (Figure), and postoperative spinal trauma in 5/7 patients. Biopsy-related deterioration persisted in 2/7 patients, with an elevated EDSS score of 7.5 (median; range 2.0-8.5) at last follow-up (mean 86.6 months after spinal biopsy; range 20-218).

Discussion

Undoubtedly, CNS biopsy represents the ultimate diagnostic step for evaluation of an unclear tissue alteration such as a longitudinally extensive spinal cord lesion. NMO histopathology in general is characterized by inflammatory, often destructive, demyelinating lesions with perivascular immunoglobulin G and complement deposition, hyalinized vessels and eosinophilic granulocytes. An astrocytic pathology with AQP4 loss extending beyond the area of demyelination is typical and oligodendrocytes may be lost within lesions.[10,11] However, invasive biopsy procedures may have adverse effects, particularly in the inflamed spinal cord. Moreover, in this case series, initial routine histopathology excluded tumors in 6/7 patients (Table), but did not lead to the correct diagnosis. Five patients experienced transient postoperative complications shortly after biopsy, leading to persistent, severe paraparesis in

one patient and permanent tetraparesis with wheelchair dependence in another. Obviously the proportion of severe post-operative complications was relatively high in our study, possibly due to the central localization of the spinal lesions as well as their inflammatory nature, leading to local hyperemia and thus an increased susceptibility to unintended bleeding events and edema. NMO-related LETM was only recognized after detection of NMO-IgG. Although histopathological reevaluation in 4 patients revealed some typical NMO features, a definite diagnosis was challenging despite familiarity with the AQP4 serostatus as certain neuropathological findings typical of NMO like perivascular depositions of activated complement were not detectable. This observation is in line with previous reports suggesting heterogeneity of NMO lesions according to lesion stage, biopsy site and the paucity of typical spinal specimen.[10,11]

Our report confirms and extends a previous single case report,[12] but has several limitations. The analysis is retrospective, and the patients were not recruited from a random population of patients with spinal lesions including confirmed cases of glioma but from a recently described cohort of NMOSD patients.[7] Moreover, 3/7 patients were biopsied in 1995 and 2002 before the availability of NMO-IgG measuring.[8] However, our findings emphasize the importance of NMO-IgG testing for LETM. Considering the possible adverse effects of biopsy procedures, testing for NMO-IgG is justified in patients with unclear spinal cord tumors. In light of the heterogeneity of available assays and the low prevalence of NMOSD, a detection method with sufficient sensitivity and specificity should be used.[13] Biopsy of longitudinally extensive spinal lesions should be limited to cases in which other tests only provide inconclusive diagnostic findings.

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Conflict of Interest Statement

- Marius Ringelstein received speaker honoraria from Novartis and travel reimbursement from Bayer Schering.
- Imke Metz received grants by Heidenreich von Siebold Program and the University Medical Center, Georg August University, Göttingen, Germany, and honoraria for lectures and travel/accommodations/meeting expenses from TEVA, Biogen Idec, Sanofi-Aventis and Bayer Health Care.
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Figure legends

Figure: **Pre- and postoperative spinal MRIs of patient #1.** (A, B) Shown is a longitudinal and space-consuming transverse myelitis between vertebral segments Th2 and Th7 before diagnostic biopsy. The T2w image shows a particular swelling of the spinal lesion (A, white arrow heads) and the T1w image a low contrast Gadolinium enhancement (B, white arrows). Images (C) and (D) illustrate the postoperative state after spinal biopsy at level Th5. Epidural bleeding occurred at levels Th4-Th7 with ventral dislocation and compression of the myelon (open white arrows in T2w- (C) and STIRw- (D) images).

Supplemental Figure: **Histology of spinal NMO lesion of patient #6.** Shown here is a destructive inflammatory demyelinating lesion with AQP4 loss. A small specimen is available for analysis from an eloquent lesion location within the spinal cord (A; HE). Higher magnification shows a destructive, loose-textured lesion with numerous macrophages (B; HE) and a T cell infiltrate (C; anti-CD3). Only few axons are preserved, underlining the destructive nature of the lesion (D; anti-NF200). Although the myelin is partially preserved (E; anti-PLP), higher magnification clearly shows myelin degradation products within macrophages, indicating active demyelination (F; anti-MBP; arrows indicate macrophages with myelin debris). Astrocytes appear partially dystrophic and partially depleted (G; anti-GFAP; arrow indicates dystrophic astrocyte), whereas AQP4 staining of astrocytes is completely lost (H; anti-AQP4). Macrophages show AQP4-positive degradation products within their cytoplasm (H; brown-colored macrophages). Scale bars: A: 500 µm; B-D: 100 µm; E: 200 µm; F+G: 50 µm; H: 100 µm.

Table: Cohort of patients with spinal biopsy due to presentation with longitudinally extending spinal cord lesions (LESCL).

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7
Age at onset, sex, origin	52, female, Caucasian	24, female, Caucasian	45, female, Caucasian	44, female, Caucasian	47, female, Caucasian	31, female, Afro-American	36, female, Caucasian
Age at LESCL/biopsy	52	29	47	57	50	31	36
Timespan first symptom to biopsy	2 months	64 months	19 months	144 months	33 months	0.25 month (8 days)	4.5 months
Timespan from LESCL onset to biopsy	2 months	1.5 months	10 months	1 month	0.25 month (8 days)	0.25 month (8 days)	4.5 months
ON or myelitis as initial event (date)	Myelitis (01/2011)	ON (10/1989)	Myelitis (05/2001)	Rhombencephalitis (1995)	ON (10/2005)	Myelitis (10/2011)	Myelitis (11/2001)
Optic neuritis	Never	2x left, 2x right before biopsy	2x after biopsy (once bilateral, once left)	Never	2x before biopsy (10/2005 + 12/2006)	Never	1x after biopsy (10/2003)
LESCL symptoms	Feet numbness, paraparesis (BMRC: 5-/5), spinal ataxia, beltlike thoraco-lumbar dysesthesia, sensory function loss below Th6	Spastic paraparesis (BMRC: 4+/5), tetraataxia, voiding dysfunction, back pain, sensory function loss below Th5	Gait disturbances, slight tetraparesis (BMRC: 4+/5), sensory function loss below C1	Dysesthesia at occiput, right sided sensorimotor deficit	Severe paraparesis, sensory function loss below Th3, voiding dysfunction	Back pain, paraparesis, sensory function loss below Th4, voiding and defecation dysfunction	Right sided foot and big toe extension palsy, back pain, gait instability
Cerebral MRI at LESCL	Multiple WML, Gd-; most likely microangiopathic	Normal	Normal	Normal	Unspecific WML	Few unspecific gliotic changes	Normal
Spinal MRI of LESCL	Th2-7, slight Gd+, longitudinally extensive centrally located lesion with cord swelling	C2-6, focal Gd+, longitudinally extensive dorsally located lesion with cord swelling	C1-7, focal Gd+, longitudinally extensive dorsally located lesion with mild cord swelling	Medulla oblongate-C4/5, Gd-, longitudinally extensive centrally located lesion	Th1-5, focalGd+, longitudinally extensive ventrally located lesion with cord swelling	C7-Th6, focal Gd+, longitudinally extensive centrally located lesion with mild cord swelling	C2-Th9, focal Gd+, longitudinally extensive centrally located lesion with cord swelling
CSF at LESCL, OCB pattern	4 cells/µl, Type 4	2 cells/µl, Type 1	6 cells/µl, Type 1	Minimal pleocytosis, Type1	25 cells/µl, n.a.	51 cells/µl, Type 3	10 cells/µl, Type 1
EDSS prior biopsy	2.5	3.5	2.5	4.0	5.5	7.5	8.0
Suspected diagnosis prior to biopsy	Astrocytoma, Ependymoma	Atypical pen like glioma	Tumor of unknown etiology	Spinal tumor	Spinal glioma (astrocytoma)	Intramedullary tumor	Intramedullary tumor
Acute treatment of spinal cord lesion	Dexamethasone, oral prednisolone, performed after spinal cord biopsy	IV steroid pulse, transient good improvement	Ceftriaxone, IV steroid pulse, IVIG, transient improvement	IV steroid pulse, no improvement	IV steroid pulse, transient minor improvement	IV steroid pulse, performed after spinal cord biopsy	IV steroid pulse, minor improvement
Biopsy site (date)	Th5 (03/2011)	C3 (03/1995)	C4 (12/2002)	C2-6 (09/2007)	Th3 (07/2008)	Th4 (10/2011)	Th2 (03/2002)

Postoperative complications	Epidural hematoma (requiring surgical revision), paraplegia	None	Slight increase of leg weakness and numbness	CSF leakage (3 surgical revisions), tetraparesis	Paraplegia	Paraplegia	None
Initial histopathology	Inflammatory, destructive CNS lesion	Gliogenic tumor with desmoplastic angiogenic compound of low malignancy; DD atypical glioma	Presumed angiodysgenetic necrotizing myelopathy Foix-Alajouanine	Subacute necrosis in clearence, definitively no tumor	Tumor free spinal cord (no clear diagnosis possible)	CNS tissue with severe reactive and resorptive changes. No neoplasia.	Reactive CNS-tissue with inflammatory and resorptive changes
AQP4-Ab tests (CBA) after biopsy	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Final diagnosis at last follow-up	AQP4-Ab positive LETM	AQP4-Ab positive NMO	AQP4-Ab positive NMO	AQP4-Abpositive LETM	AQP4-Ab positive NMO	AQP4-Ab positive LETM	AQP4-Ab positive NMO
EDSS at last follow-up /months after biopsy	2.0/25 months	8.0/218 months	8.5/121 months	7.5/69 months	8.0/23 months	4.0/20 months	4.5/130 months
Time from first symptom to final diagnosis	2.5 months	144 months	30 months	160 months	34 months	0.5 month	108 months
Time from biopsy to final diagnosis	0.5 month	80 months	11 months	16 months	1 month	0.25 month	103.5 months
Medication at last follow-up	Rituximab	Rituximab	Rituximab, low dose steroids	IVIG, low dose steroids	Rituximab	Rituximab	Rituximab

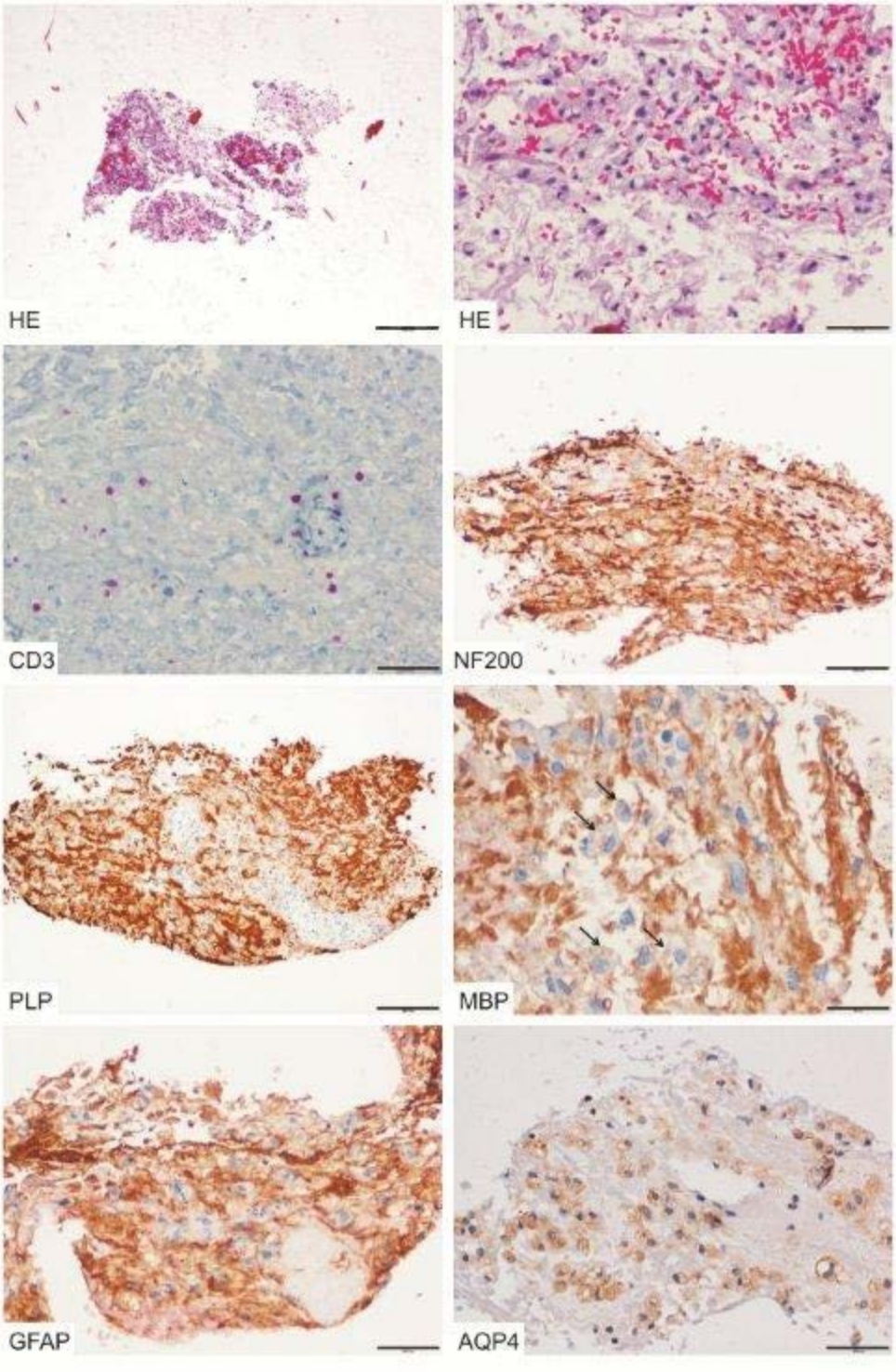
Abbreviations: AQP4-Ab: aquaporin4-antibody; BMRC: British Medical Research Council; C: cervical; CBA: cell based assay; CNS: central nervous system; CSF: cerebrospinal fluid; EDSS: Expanded Disability Status Scale; Gd: gadolinium; IV: intravenous; IVIG: intravenous imunoglobulins; LESCL: longitudinally extending spinal cord lesion; LETM: longitudinally extensive transverse myelitis; LFB: Luxol Fast Blue; MRI: magnetic resonance imaging; n.a.: not available; OCB: oligoclonal bands; ON: optic neuritis; Th: thoracic; WML: white matter lesions.
Oligoclonal bands patterns (OCB-P): Pattern 1 = no OCBs in CSF and serum; pattern 2 = OCBs in CSF but not serum (intrathecal IgG synthesis); pattern 3 = OCBs in CSF but not serum (intrathecal IgG synthesis) plus additional identical OCBs in CSF and serum; pattern 4 = identical OCBs in CSF and serum (systemic immune reaction).

A

B

C

D


HE
HE
CD3
NF200
PLP
MBP
GFAP
AQP4